

THE SYNTHESIS OF SUBSTITUTED
BENZOFURANS AND DIHYDROBENZOFURANS

BY

MICHAEL WITTE

B.S., Loyola University, Chicago, 1937

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SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
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INTRODUCTION

Previous investigators have established the structural formula of rotenone.¹ It has a fused ring system composed of two benzene nuclei and three heterocyclic oxygen containing rings and three substituents, two methoxyl and one isopropenyl group. Since the supply of rotenone is limited, it would be desirable to develop methods for synthesizing compounds containing certain combinations of the ring systems present in rotenone, which would have insecticidal action.

The purpose of the present investigation was to study the synthesis of properly substituted coumaranones, benzofurans and dihydrobenzofurans. Specific attention was directed toward the synthesis of some of the degradation products of rotenone; viz. isotubanol, isotubaic acid and their dihydro derivatives.

EXPERIMENTAL

4-Hydroxy-2-isopropylidinecoumaran-3-one:—A mixture of 10 g. of 4-hydroxycoumaran-3-one, 35 c.c. of dry acetone, 25 g. of powdered potassium hydroxide and 300 c.c. of absolute ethanol was shaken for 36 hours at room temperature. The green solution turned red after 20 hours shaking. At the end of the reaction time, the red precipitate was filtered and carefully acidified with 50 c.c. of 6 *M* hydrochloric acid. A yellow precipitate was obtained by this treatment. This was filtered and recrystallized twice from acetone to give a yield of 10.5 g. of orange prisms melting at 121°. The yield was 83 percent of the theoretical.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.47; H, 5.26

Found: C, 69.25; H, 5.66

4-Benzoxo-2-isopropylidinecoumaran-3-one:—A mixture of 200 mg. of 4-hydroxy-2-isopropylidinecoumaran-3-one, 1 c.c. of benzoyl chloride, 10 c.c. of water, 10 c.c. of acetone and 1.5 g. of sodium carbonate was refluxed for one hour. The hot solution was then poured into a mixture of ice and water with hand stirring. Yellow crystals separated at stand-

ing. These were filtered and recrystallized from ethyl acetate. Yellow needles were obtained melting at 160° . The yield was 280 mg. which was 90.5 percent of the theoretical.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.76

Found: C, 73.74; H, 5.02

2-Isopropyl-3-hydroxy-4-benzoxidihydrobenzofuran and Isotubanol Benzoate:- A mixture of 11.5 g. of 4-benzoxo-2-isopropylidinecoumaran-3-one, 0.5 g. of platinum oxide, 300 c.c. of absolute ethanol and 4 drops of concentrated hydrochloric acid was shaken with hydrogen at an initial pressure of 48 pounds and at room temperature. The reaction mixture was removed when approximately 2 moles of hydrogen was taken up. The mixture was filtered and the ethanol was removed by distillation at 30 mm. and 30° . A yellow oily residue was obtained and could not be crystallized. The oil was then distilled at 3 mm. Three sharp cuts were obtained. At 65° , a few drops of a colorless pine smelling oil came over. At 105° - 110° a very small amount of a colorless oil which soon crystallized was obtained. These two compounds were not characterized. At 175° - 180° , 8 g. (73 percent) of a yellow oil came over. This compound proved to be the benzoate of isotubanol.

Since the benzoate of isotubanol was obtained, obviously upon distillation at 175° - 180° , a molecule of water split out from the 2-isopropyl-3-hydroxy-4-benzoxidihydrobenzofuran, which originally was formed in the reduction.

Isotubanol:- A mixture of 8 g. of isotubanol benzoate, 400 c.c. of 95 percent ethanol and 60 c.c. of 10 percent aqueous sodium hydroxide was refluxed 2 hours. At the end of this time, 350 c.c. of ethanol was distilled off, the mixture was cooled and then treated with an excess of solid carbon dioxide. It was then extracted five times with 30 c.c. portions of diethyl ether. The ether solution was dried over anhydrous sodium sulfate, filtered and the ether was distilled, leaving a yellow oil. This oil was distilled and at 170° and 3 mm. pressure a colorless oil came over. This was isotubanol. The yield was 4 g. (79 percent). This compound gave no test with ferric chloride.

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87

Found: C, 75.18; H, 7.00

Isotubaic Acid:- Two-tenth of a gram of metallic sodium was placed in 2 c.c. of dry methanol in a bomb of 35 c.c. capacity. After the initial

reaction of the sodium and the methanol had taken place, 0.3 g. of isotubanol and 5 g. of solid carbon dioxide were added. The bomb was closed tightly and placed in an oil bath. The bath was heated to 180° and kept at that temperature for 2 hours. The bomb was then removed and cooled. The contents were washed out with 20 c.c. of distilled water. The aqueous solution was carefully acidified with hydrochloric acid. The cloudy mixture was then extracted four times with 25 c.c. portions of diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate, filtered and the ether was removed by distillation to leave a pasty residue. The residue was taken up in 20 c.c. of boiling toluene, the solution filtered and cooled in an ice salt mixture. Long white needles of the acid were obtained which melted at 183° . The yield was 0.3 g. (86.5 percent). The melting point agreed with that recorded by Reichstein and Hirt.² A mixed melting point with a sample of isotubaic acid obtained from the degradation of rotenone showed no depression.

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.42; H, 5.49

Found: C, 65.39; H, 5.57

Dihydrotubanol Hexahydrobenzoate:- A mixture of 4.5 g. of 2-isopropylidene-4-benzoxycoumaran-3-one, 0.25 g. of platinum oxide, 4 drops of concentrated hydrochloric acid and 100 c.c. of absolute ethanol was shaken with hydrogen at an initial pressure of 42 pounds at room temperature. The shaking was continued until no more hydrogen was taken up. The reaction mixture was then filtered. The ethanol was removed by distillation at 30° and 30 mm. to leave a yellow oil. This was distilled at 2 mm. pressure. A few drops of a colorless oil came over at 72° . This was not characterized. At 170° a colorless oil was obtained. The yield was 3 g. (68 percent of the theoretical).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.94; H, 8.36

Found: C, 74.89; H, 8.22

Dihydrotubanol:- A mixture of 2 g. of the hexahydrobenzoic ester, 25 c.c. of ethanol, 10 c.c. of water and 10 c.c. of 10 percent of aqueous sodium hydroxide was refluxed 1.5 hours. The mixture was cooled, then treated with an excess of dry carbon dioxide. The resulting solution was then extracted four times with 25 c.c. portions of diethyl ether which was dried over anhydrous sodium sulfate. The ether was evaporated leaving an oily residue. Vacuum distillation yielded dihydrotubanol as a color-

less oil which boiled at 134° at 4 mm. Its properties agreed with those previously recorded.³

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.08; H, 7.96

Found: C, 73.71; H, 8.09

SUMMARY

The synthesis of isotubaic acid was effected by the following sequence of reactions: resorcinol $\rightarrow$ 4-methyl-7-hydroxycoumarin $\rightarrow$ 4-methyl-7-acetoxycoumarin $\rightarrow$ 4-methyl-7-hydroxy-8-acetocoumarin $\rightarrow$ 2,6-dihydroxyacetophenone $\rightarrow$ 2,6-diacetoxyacetophenone $\rightarrow$ 2,6-diacetoxy-w-bromoacetophenone $\rightarrow$ 2,6-dihydroxy-w-bromoacetophenone $\rightarrow$ 4-hydroxycoumaran-3-one $\rightarrow$ 2-isopropylidene-4-hydroxycoumaran-3-one $\rightarrow$ 2-isopropylidene-4-benzoxycoumaran-3-one $\rightarrow$ 2-isopropyl-3-hydroxy-4-benzoxydihydrobenzofuran $\rightarrow$ isotubanol benzoate $\rightarrow$ isotubanol $\rightarrow$ isotubaic acid.

This synthetic acid was found to be identical with isotubaic acid obtained from the alkaline scission of rotenone.

Dihydrotubanol was synthesized as follows: 2-isopropylidene-4-hydroxycoumaran-3-one $\rightarrow$ 2-isopropylidene-4-benzoxycoumaran-3-one $\rightarrow$ 2-isopropyl-4-hexahydrobenzoxycoumaran $\rightarrow$ dihydrotubanol.

A study of catalytic hydrogenations of 4-hydroxycoumaranones showed that when ethanol was the solvent, a trace of hydrochloric acid was required to effect reduction of the coumaranone carbonyl group. It was found that hydrochloric acid labilized the aromatic ring and stabilized the heterocyclic ring toward hydrogen.

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VITA

The author was born in New York, N. Y., on March 15, 1911. He received his elementary education in Benton School and Central High School of Kansas City, Mo. He obtained a B.S. degree from the University of Loyola, Chicago, in 1937. In the fall of that year he entered the Graduate School of the University of Illinois and obtained the degree of M.S. in 1938. He has held the appointment of Assistant in Chemistry during the school years of 1938, 1939, and 1940.



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